REMARKS

I. Status of the Claims

Claims 1-69 were originally filed. In response to a restriction requirement, claims 1-10, 22, and 23 have been elected, whereas the non-elected claims have been canceled. In the Office Action of October 6, 2004, the Examiner discussed only claims 1-9, 22, and 23. Applicants surmise that claim 10 was inadvertently left out and respectfully request the Examiner's clarification regarding the status of this claim.

II. Claim Rejections

A. 35 U.S.C. §101 and 35 U.S.C. §112, First Paragraph

Claims 1-9, 22, and 23 were rejected under 35 U.S.C. §101 for alleged lack of either a well-established utility or a credible specific and substantial asserted utility. Applicants respectfully traverse the rejection.

1. Standard to Assess Utility

According to MPEP §2107, the Examiner should review the claims and the supporting written description to determine whether the utility requirement under 35 U.S.C. §101 is met. No rejection based on lack of utility should be made if an invention has a well-established utility, *i.e.*, a utility that will be immediately appreciated by one of ordinary skill in the art based on the characteristics of the invention, regardless any such utility has been asserted. Neither should any rejection be made for lack of utility if an applicant has asserted a specific and substantial utility that would be considered credible by one of ordinary skill in the art.

In most cases, an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101. MPEP §2107.02 III A. The Court of Customs and Patent Appeals stated in *In re Langer*:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of §101 for the entire claimed subject matter unless there is a reason for one

> skilled in the art to question the objective truth of the statement of utility or its scope.

In re Langer, 183 USPQ 288, at 297 (CCPA, 1974, emphasis in original). To overcome the presumption of sufficient utility as asserted by an applicant, the Examiner must carry the initial burden to make a *prima facie* showing of lack of utility and provide a sufficient evidentiary basis for the conclusion. In other words, the Examiner "must do more than merely question operability--[he] must set forth factual reasons which would lead one skilled in the art to question objective truth of the statement of operability." *In re Gaubert*, 187 USPQ 664, 666 (CCPA 1975).

MPEP §2107.02 IV further states, a detailed explanation should be given for a utility rejection as to why the claimed invention has no specific and substantial asserted utility. Documentary evidence should be provided when possible. Otherwise the Examiner should specifically explain the scientific basis for his factual conclusions.

2. The Asserted Utility Is Specific and Substantial

The present specification provides, for the first time, the polynucleotide sequence and amino acid sequence of human Slo2 and Slo4, two polypeptide subunits of a Slo family potassium channels with the characteristics of voltage-gating. Pending claims are drawn to nucleic acids encoding Slo4 polypeptides, a new member of the Slo family and the Slo2/4 subfamily. It is specifically asserted that the Slo2 and Slo4 channels coded by the claimed nucleic acids "contribute to the modulation of neuronal excitability," and are "involved in action potential repolarization and refractory period and the control of neurotransmitter release" and "regulating muscle contraction, heart rate, airway tone, inflammation, and lymphocyte proliferation" (*see, e.g.*, page 11, lines 5-13, of specification). The specification also states that modulators of Slo2 and Slo4 are useful for "treating disorders of neuronal excitability related to increased levels of neuronal activity or abnormal neurotransmitter release," for example, "neuropathic pain, epilepsy and seizure disorders, depression and other psychotic disorders such as bipolar disease and schizophrenia, migraine and anxiety" (*see, e.g.*, page 11, lines 13-23). Furthermore, the specification asserts that the availability of amino acid and polynucleotide

sequences of these potassium channel subunits would enable assay systems to identify activators and inhibitors of potassium channels comprising these subunits, which may be used for treating neurological and other conditions related to the physiological functions of these potassium channels, such as central nervous system (CNS) disorders, cognitive disorders, cardiac arrhythmia, *etc.* (*see, e.g.*, page 11, lines 24-34).

Applicants assert that the present invention has a specific utility. Specific utility is defined by the MPEP as a utility that is specific to the subject matter claimed. The MPEP explains that applications show sufficient specific utility when applicants disclose a "specific biological activity" and reasonably correlate that activity to a "disease condition." MPEP §2107.01 and §2107.02. In the present application, Applicants disclose a "disease condition," *i.e.*, altered neuronal excitability or abnormal neurotransmitter release, that correlates with a "biological activity," *i.e.*, the opening and closing of voltage-gated potassium channels. This application demonstrates that the Slo channels are voltage-gated potassium channels that modulate cellular excitability. The application further provides methods for identifying compounds capable of modulating Slo channel activities, which may be used for treating diseases related to abnormal neurological reactions. Applicants thus submit that the present invention has a specific utility, *e.g.*, the Slo channels can mediate neuronal cell excitability in the CNS and in peripheral tissues, which is clearly specific for the claimed Slo potassium channels and not any ion channels.

Applicants also assert that the present invention has a substantial utility or a "real-world" use. The present invention provides voltage-gated potassium channels comprising a Slo2 or Slo4 alpha subunit, demonstrates that Slo channels modulate cellular excitability, and teaches how to identify activators or inhibitors of these Slo channels. Therefore, there is a real-world use of the invention in the modulation of cell excitability, as well as in the identification of compounds that modulate Slo potassium channels and thus can be useful as therapeutic agents for treating diseases related to altered cell excitability and abnormal neurotransmitter release, including various conditions of the central nervous system or peripheral tissues.

3. The Asserted Utility Is Credible to One of Skill in the Art

In a 37 C.F.R. §1.132 declaration accompanying this response, Dr. Ken McCormack, a scientist with extensive experience studying various ion channels, attests that given the description of human Slo2 and Slo4 potassium channels in the present application, one of skill in the art would find the asserted specific and substantial utility credible.

Specifically, Dr. McCormack states that the Slo2 and Slo4 channels are voltage-gated potassium channels highly expressed in the central nervous system (CNS). Since these potassium channels begin to activate in a voltage range below the typical thresholds for action potential generation, one of skill in the art would reasonably believe that the channels are involved in modulating cell excitability. Because of their high level of expression in the CNS, an artisan would also reasonably believe that these channels can serve as therapeutic targets for treatment of conditions related to altered neuronal excitability in the CNS, *e.g.*, epilepsy, migraines, and psychotic disorders. The identification of the Slo2 and Slo4 channels therefore has a substantial utility, or a "real world" use, since this discovery makes possible the routine identification of activators and inhibitors of the Slo2/Slo4 channels, which may be used as therapeutic agents for treating conditions caused by or related to abnormalities in neuronal excitability. Dr. McCormack further states that since this asserted utility relies on the expression of Slo2/Slo4 channels in the CNS and their involvement in the regulation of cell excitability, which are specific features of these potassium channels and not a broad class of ion channels, the present invention thus has a specific utility. See paragraph 6 of the declaration.

In addition, Dr. McCormack points out in his declaration that regulation of ion channel activity is a therapeutic approach often taken in cases where the targeted channel itself does not cause the condition being treated. Dr. McCormack states in paragraph 8 of the declaration that,

> There are known instances where modulation of an ion channel is useful for treating a specific disease even though the ion channel itself may not cause the disease. For example, hypertension can be caused by a variety of illnesses such as renal disease and diabetes. Among the treatment strategies for hypertension is the use of drugs such as calcium channel blockers

to relax the vasculature. Relaxing the vasculature to reduce blood pressure is useful and effective, even if the original cause of the hypertension is unrelated to vascular tone. Similarly, it is perfectly reasonable to expect that the targeting of a Slo2/Slo4 potassium channel, a voltage-gated potassium channel highly expressed in the CNS and involved in regulation of neuronal cell excitability, is an appropriate strategy for treating neurological disorders related to abnormal excitability of the cells, whether or not such abnormality is directly caused by altered Slo2/Slo4 channel activity. Thus, the asserted utility of the Slo2/Slo4 potassium channel of the present application is reasonable and therefore credible to an ordinarily skilled artisan.

Thus, a causal relationship between the claimed Slo potassium channels and diseases or conditions to be treated is not necessary for the asserted utility of the ion channels.

Applicants believe that, by way of an expert's declaration pursuant to 37 C.F.R. §1.132, it has been properly established that the asserted utility of the claimed Slo channels is not only specific and substantial, but also credible to one of skill in the art.

4. The Examiner Has Not Established A *Prima Facie* Showing of Lack of Utility

The Examiner's rejection of the pending claims for alleged lack of utility was based on the repeated statement that no evidence in the specification or prior art demonstrates a physiological function of the K^+ channels in controlling cell excitability or a correlation of the claimed ion channels to a disease state. Simply put, the Examiner did not believe the specific and substantial utility asserted by Applicants.

Raising a rejection for lack of utility in such a manner is inconsistent with the proper practice described in the MPEP, which places the initial burden on the Examiner, not Applicants, to provide evidence to support a factual conclusion of the credibility of an asserted utility. In fact, MPEP §2107.02 III.B. specifically cautions Office personnel that, once an assertion of a particular utility is made, "that assertion cannot simply be dismissed ..... as 'wrong,' even when there may be reason to believe the assertion is not entirely accurate." Instead, the Examiner must provide an explanation setting forth the reasoning used in concluding that the asserted specific and substantial utility is not credible; support for factual findings relied

upon in reaching the conclusion; and an evaluation of all relevant evidence of record, including utilities taught in the closest prior art. MPEP §2107.02 IV.

The Examiner provided none of the above. Instead, the Examiner repeatedly questioned Applicants' assertions regarding the utility of this invention. For instance, the Examiner expressed his doubts about the asserted use of the claimed Slo2/Slo4 channels as therapeutic targets for treating a variety of neurological conditions and disorders named in the application since "defective forms [of the claimed potassium channels] are not disclosed" (see page 5 of the Office Action of October 6, 2004). The Examiner also apparently based his disbelief on the argument that since the specification "does not disclose a correlation between any specific disorder and an altered level or form of the claimed polynucleotides" or "whether the claimed polynucleotides would be over expressed or under expressed in a specific, diseased tissue," any therapeutic approach targeting the Slo2/Slo4 ion channels cannot be placed in use and, therefore, no real-world utility is established. Applicants cannot agree with this reasoning. As discussed in the previous section, Dr. McCormack has clearly illustrated in his declaration that for an ion channel to be useful as a therapeutic target, it need not be the direct cause of a condition or disease. Thus, Applicants do not believe that, in light of the 37 C.F.R. §1.132 declaration, there remains any reasonable basis for the Examiner to continue doubting the credibility of the asserted specific and substantial utility of the claimed Slo2/Slo4 channels.

Applicants respectfully submit that a *prima facie* showing of lack of utility is not established and the withdrawal of the utility rejection is therefore respectfully requested.

5. Claims Drawn to Nucleic Acids Encoding Fully Characterized Proteins Meet the Utility Requirement under 35 U.S.C. §101

The Slo channels of the present invention are fully characterized both structurally and functionally. The polynucleotide sequences encoding the Slo4 polypeptides are defined by shared structural features of the Slo4 polypeptides, *e.g.*, their coding sequences are capable of hybridizing to a reference sequence under specified conditions, and shared functional features, *e.g.*, capable of forming a voltage-gate potassium channel with another alpha subunit.

According to *the Revised Interim Utility Guidelines Training Materials* promulgated by the PTO (http://www.uspto.gov/web/menu/utility.pdf), a characterized protein has sufficient utility for patentability. This standard is made evident from Example 8 of the guidelines. In Example 8, a compound A is disclosed to inhibit enzyme XYZ, a well known enzyme, *in vitro*. The specification states that the compound A can be used to treat diseases caused or exacerbated by enzyme XYZ. No such diseases are named. Claim 1 is directed to compound A. Claim 2 is directed to a method of treating a disease caused or exacerbated by enzyme XYZ consisting of administering an effective amount of compound A to a patient. In the subsequent analysis, claim 2 is deemed insufficiently supported by a real world context of use. This is because neither the specification nor the art of record discloses any disease or conditions caused or exacerbated by enzyme XYZ and therefore, the asserted utility is seen as a method of treating an unspecified and undisclosed disease or condition, which does not define a "real world" context of use. Claim 1, however, is regarded as having utility because claim 1 is directed to a compound that inhibits an enzyme and enzymes have well established utility in the art, *i.e.*, catalyzing certain reactions.

This example can be compared to the present application. The present application claims nucleic acids encoding subunits of Slo potassium channels, which are analogous to compound A that inhibits enzyme XYZ. The specification states that Slo channels are likely involved in modulating cell excitability in the nervous system and other tissues such as heart and muscle. Thus, the ion channels can be used to as targets for treating disorders related to cell excitability. In Example 8, claim 1 directed to compound A is found to have utility even though there is no disclosure of specified disease that to be treated. Accordingly, even if the Examiner is not convinced, despite the disclosure by the present specification, that the Slo channels are involved in regulation of cell excitability in certain tissues, a claim directed to compound A, *i.e.*, the nucleic acids encoding the Slo potassium channel subunits in the present case, have sufficient utility for patentability. The utility resides in the fact that the claimed nucleic acids encode subunits of voltage-gated potassium channels, which, like enzymes, have a well-established utility in the art: adjusting the passage of K^+ according to varying conditions.

Analysis of pending claims according to *the Revised Interim Utility Guidelines Training Materials* therefore further supports Applicants' position that the rejection for lack of utility is improper.

In summary, Applicants believe that the rejection for lack of utility is improper and respectfully request its withdrawal.

B. 35 U.S.C. §112, First Paragraph

Claims 1-9, 22, and 23 were also rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement, as the Examiner alleged that since the claimed invention has no utility under 35 U.S.C. §101, one of skill in the art would not know how to use it. Since the forgoing discussion has established a specific and substantial asserted utility, Applicant believes that the utility-based enablement rejection should be properly withdrawn.

C. 35 U.S.C. §102

Claims 1-9, 22, and 23 were rejected under 35 U.S.C. §102(e) for alleged anticipation by Cutis *et al.* (US 2003/0143675). Applicants respectfully traverse the rejection in light of the Rule 131 declaration filed herewith.

To anticipate a pending claim, a prior art reference must provide, either expressly or implicitly, each and every limitation of the pending claim. MPEP §2131. The pending claims are directed to an isolated nucleic acid encoding a Slo4 polypeptide comprising an alpha subunit of a Slo potassium channel. This Slo4 polypeptide has the following properties: (i) it forms, with at least one additional alpha subunit, a potassium channel comprising the characteristic of voltage-gating; and (ii) it can hybridize under stringent hybridization conditions to a nucleic acid encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:4. The Examiner asserted that the Curtis reference discloses a nucleic acid encoding SEQ ID NO:58, which is about 97% identical to SEQ ID NO:4, and therefore anticipates the pending claims.

Applicants submit that the rejection is improper because the Curtis reference could be entitled to an effective filing date no earlier than July 31, 2000. By way of a Rule 131 declaration and accompanying evidence, Applicants establish that this date is later than the time

when the present inventors first completed the claimed invention. The Curtis reference claims priority to a large number of U.S. patent applications and provisional applications, earliest of which has a filing date of May 12, 2000. A careful review of USSN 60/215,376, the second earliest priority documents with a filing date of June 29, 2000, reveals that SEQ ID NO:58 of the Curtis reference is not present. In fact, USSN 60/215,376 describes only SEQ ID NO:1-5, which correspond to SEQ ID NOs:4, 5, 6, 9, and 8 of the Curtis reference, respectively. Thus, even if ***assuming*** that SEQ ID NO:58 of the Curtis reference is disclosed in the third earliest priority document (USSN 60/221,769, filed July 31, 2000), where SEQ ID NO:58 is concerned, the Curtis reference has an effective filing date no earlier than July 31, 2000.

In contrast, in the Rule 131 declaration by the named inventors, Dr. Timothy Jegla and Dr. Julie Dickson Witzel attest with evidence to establish that ICAgen scientists had obtained the polynucleotide coding sequences and corresponding amino acid sequences of human Slo2 and human Slo4 before July 31, 2000. It is thus established that the subject invention was completed in the United States prior to July 31, 2000. As such, Applicants submit that the Curtis *et al.* reference is not available as §102(e) art against the pending claims. Accordingly, the withdrawal of the anticipation rejection is respectfully requested.

III. Priority

The Examiner asserted that USSN 60/249,112, to which the present application claims priority, does not adequately support claims 1-9, 22, and 23 of this application. The Examiner appeared to take the position that the priority document is not enabling due to the alleged lack of patentable utility of the invention described. Applicants respectfully disagree with the Examiner. USSN 60/249,112 fully and accurately discloses the polynucleotide and polypeptide sequences for human Slo2 and Slo4 (*see, e.g.*, pages 74-76 of USSN 60/249,112), describes the characteristics of the potassium channels (*see, e.g.*, Examples 1 and 2 on pages 65-73), and asserts their utility as a therapeutic target for treating neurological or other conditions (*see, e.g.*, page 11), this application thus provides full support for the present application in the substance disclosed. As far as utility-based enablement is concerned, Applicants believe that the above discussion has already properly established utility under 35 U.S.C. §101 for the claimed

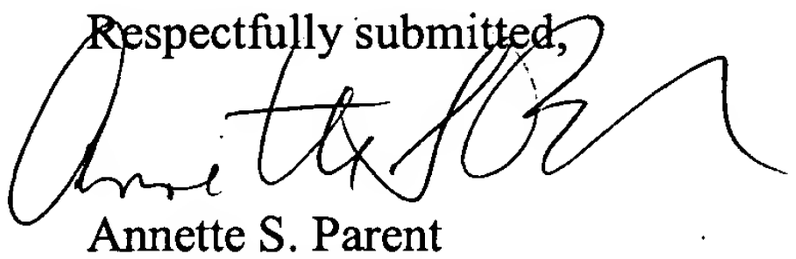
invention, the application therefore does not fail to enable for utility reasons. The withdrawal of the objection to the priority claim is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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